Remarks

Claim 1-6 are currently pending in the application.

Discussion of the 35 U.S.C. § 103(a) Rejection(s)

The rejection of claims 1, 2, 5, and 6 under 35 U.S.C. § 103(a) as being obvious over Bacus (U.S. 5,288,477) ("Bacus I") in view of the abstract of Bacus *et al.* (Breast Cancer Research and Treatment, 1999, vol.57, page 55) ("Bacus II"); Warri *et al.* (J. Nat'l Cancer Inst., 1993, vol. 85, pp. 1412-1418) ("Warri"); the abstract of Wu (Cancer Res., 1996, vol. 16, pp. 2233-2239) ("Wu"); the abstract of Fornier *et al.* (Oncology, 1999, vol. 13, pp 647-658) ("Fornier") and the abstract of Lebwohl *et al.* (Annals of Oncology, 1999, 10 suppl. 6, pp 139-146) ("Lebwohl") was maintained. Applicant respectfully traverses this rejection.

An analysis for obviousness requires a determination of the scope and content of the prior art, that the differences between the prior art and the claims at issue be ascertained, and that the level of ordinary skill in the pertinent art be understood. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Applicant provided an analysis of the scope and content of the prior art cited by the Office Action in the Response to Office Action Mailed June 4, 2004, filed December 4, 2004. The Office apparently agrees with Applicant that none of the references cited in support of this rejection, *that is* Bacus I, Warri, Wu, Fornier, Lebwohl, and Bacus II, affirmatively teach or suggest the instantly claimed method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. The Office apparently takes the position, however, that the teachings of these references in combination motivate the skilled worker to achieve the claimed invention, *and* provide the worker with a reasonable expectation of success. Applicant respectfully disagrees for the reasons set forth herein.

In response to the continuing assertion of this ground of rejection in the Final Office Action, Applicant emphasizes the clear mandate of the patent statutes and the relevant and extensive case law concerning obviousness, as well as the internal guidelines of the Patent Office itself, that "[t]he following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined."

M.P.E.P. § 2141 (citing *Hodosh v. Block Drug Co.*, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986)). Applicant respectfully contend that, at the least, the Office Action has impermissibly failed to consider the claimed invention as a whole, and has failed to establish that even *if* the references *could* have been combined (*i.e.*, that there was teaching, suggestion or motivation in the cited references themselves *to* combine) there would have been no reasonable expectation of success of arriving at the claimed invention before Applicant's disclosure. At its best, the Office Action may support an argument that the claimed invention was obvious to try, which has been expressly rejected as the standard for obviousness under 35 U.S.C. § 103. M.P.E.P. § 2145(X)(B).

For the Examiner's convenience, Applicant reiterates the salient features of the claimed invention here. This invention is directed to methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual, wherein said

method comprises collecting a tissue or cell sample from an individual both before and after exposing the individual to a chemotherapeutic or chemopreventive agent, immunohistochemically staining both samples using a detectably labeled antibody directed against a biological marker associated with senescence, apoptosis, or terminal differentiation (where the pending claims are, at the moment, being examined with regard to apoptosis), measuring the optical density of the stained samples, and determining whether expression of the biological marker was increased following exposure to the chemotherapeutic or chemopreventive agent. As such, the present invention is concerned with measuring expression of the biological markers associated with senescence, apoptosis, or terminal differentiation in tissue or cell samples from an individual both before and after treatment with a chemotherapeutic or chemopreventive agent and using those results to determine if the individual actually responded to treatment.

The Office Action reiterates the previous assertion that Bacus I "teaches a method for determining the effectiveness of a therapeutic agent in the treatment of cancer," because Bacus I teaches obtaining a *single* biopsy from a human having cancer, dividing the biopsy into two portions, treating one of the two portions *in vitro* with a compound, and comparing the percentage of cells that exhibit markers of terminal differentiation in both portions after allowing both portions to grow *in vitro*. Important distinctions between the pending claims and the Bacus I reference are ignored in this analysis. For example, the instant claims require a comparison of two separate samples, obtained at separate times, both before and after treatment has occurred; in contrast, Bacus I teaches the skilled worker to obtain one sample before treatment to be divided and differentially treated. By ignoring this difference, the Office Action fails to appreciate that, in contrast to Bacus I, the sample obtained using the instantly-claimed methods are *different*

samples, *i.e.*, the prior art explicitly teaches away from this positively-recited limitation in the pending claims. In addition, as previously contended, the present invention requires obtaining tumor tissue or cell samples both *before* and *after* treatment of an individual with a chemotherapeutic or chemopreventive agent. While the Office Action dismisses this difference as "one of *in vitro* versus *in vivo* exposure of tumor cells to a therapeutic agent," and states without reference to any teaching in the art that one of skill in the art would *always* (which seems unlikely) be motivated to extend *in vitro* methods of treating tumor cells to *in vivo* methods (provided that, again without any support or evidence that it existed, there was a reasonable expectation of success), this argument fails to address the explicit difference between that which Bacus I would teach one of skill in the art and the explicit teachings of Applicant's disclosure.

The Office Action asserts that Bacus I is analogous to the claimed invention because there is "a direct correspondence" between the *in vitro* treatment of Bacus I with the *in vivo* treatment of the claimed invention. However, it is not clear that the skilled worker would have any confidence that a method using a single sample obtained at a specific time during the course of an illness (such as cancer), which is split and then treated under laboratory controlled conditions *in vitro* using defined (and continuously-variable) concentrations of specific chemotherapeutic drugs, wherein the sample during passage *in vitro* inevitably becomes less heterogeneous as stromal cells fail to proliferate under these experimental conditions, and finally which is observed after a defined and experimentally-controlled (and precisely monitored) period of time, could give rise to any reasonable expectation that methods using different samples obtained at different times and from different points in the course of an illness such as cancer, and after treatment *in vivo* with a chemotherapeutic agent having variable and indeterminate concentrations at the sampling site and indeterminate period of contact of the agent at said site,

and that are performed on different samples, even if taken from the same site, showing variable levels of tissue heterogeneity, would be successful. Applicant has but to ask the Office to reverse the analysis and ask, would an Applicant proposing to extend *in vitro* methods to claim *in vivo* efficacy receive favorable consideration under like circumstances, to establish the inadequacy of the Patent Office obviousness determination here.

Leaving aside these important but primarily technical distinctions, Applicant reminds the Office that, in making its assessment, the claimed invention must be considered as a whole, as required by Patent Office procedures. *See* M.P.E.P. § 2141.02. In fact, the Federal Circuit has warned that "[f]ocusing on the obviousness of substitutions and differences instead of on the invention as a whole . . . [is] a legally improper way to simplify the difficult determination of obviousness." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). In *Hybritech*, the Court reversed a finding of obviousness because the large number of references (about twenty) relied upon by the lower court, when viewed as a whole, did no more than skirt around but did "not as a whole suggest the claimed invention . . . ." *Id.* In that case, the lower court had "described the claimed invention as the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay," instead of considering the invention as a whole – an improvement of an immunometric assay employing monoclonal antibodies. *Id.*

Similarly, the question in the present application is not whether the differences between the claimed invention and the teachings of the Bacus I reference would themselves have been obvious, *i.e.*, as the Office Action states, whether the difference between *in vitro* and *in vivo* would have been obvious, but rather whether the claimed invention *as a whole* would have been obvious. *See* M.P.E.P. § 2141.02. In fact, the present invention is *not* drawn to methods for *in vivo* treatment of an individual with a chemotherapeutic or chemopreventive agent, but rather to

the assessment of the response of an individual to such treatment. The Office Action improperly focused on whether it would have been obvious to substitute the *in vivo* treatment of an individual with a chemotherapeutic or chemopreventive agent for the treatment of cell cultures *in vitro* with such an agent (which is not the invention). Instead, the proper analysis is whether the claimed invention for determining the actual response of an individual to administration of a chemotherapeutic or chemopreventive agent would have been obvious in view of Bacus I, which teaches a method for *prognosticating* the effectiveness of a therapeutic agent by, among other things, removing only a single biopsy from the individual *before* treatment, and treating those cells *in vitro* with a chemotherapeutic or chemopreventive agent. Because the Office Action improperly oversimplified "the difficult determination of obviousness," *Hybritech*, 231 U.S.P.Q. at 93, the Office Action has failed to establish a *prima facie* case of obviousness based on Bacus I.

In further support of the obviousness rejection in view of Bacus I, the Office Action asserts that "[o]ne skilled in the art would *always* [which seems unlikely] be motivated to extend *in vitro* methods of treating tumor cells to *in vivo* methods of treating patients with tumors as long as there was reasonable expectation of success." *Office Action* at 5. Even if this assertion is assumed to be true (and there is neither citation nor reasoning supporting the assertion), it is telling that the Office Action never actually states that there would have been a true, actual reasonable expectation of success nor provides any citation or reasoning to support this contention. The Federal Circuit has warned against making the unwarranted *assumption* that what has been established *in vitro* will be effective *in vivo*. The Court, reversing a finding of obviousness for claims drawn to the *in vivo* use of a compound in view of published reports of *in vitro* bactericidal activity thereof, noted that "simply because a drug gives positive results *in*

vitro, it does not necessarily follow that there is a reasonable probability of success for therapeutic use of that drug *in vivo*." *In re Gangadharam*, 13 U.S.P.Q.2d 1568, 1570 (Fed. Cir. 1989) (unpublished). In *Gangadaram*, the Board had affirmed a finding of obviousness in view of one reference, authored by the applicant, because "the teachings of Gangadharam considered as a whole would clearly have led one of ordinary skill in the art to use [the compound] in the treatment of mammals infected with *M. tuberculosis* bacteria or *M. intracellularare* bacteria (as claimed here) with at least a reasonable expectation of success." *Id.* at 1568. The Federal Circuit rejected this argument because the use of a general reference of positive results "in an entirely different context, *in vitro*, than which is claimed, and precatory, encouraging statements relating to uncertain future investigations and possible results," did not meet the statutory burden of *prima facie* case of obviousness. Further, the Court stated that the attempt to show that the reference "would have provided to one of ordinary skill in the art a reasonable expectation [of success] fell woefully short of its burden." *Id.* at 1569. There are numerous other examples where the Board has also come to similar conclusions about *in vitro* results not being predictive of *in vivo* efficacy. *See, e.g.*, *In re Anderson*, 30 U.S.P.Q.2d 1866, 1870 (B.P.A.I. 1993) ("We question whether one skilled in the art would accept appellants' '*in vitro*' test as predictive of '*in vivo*' results . . . ."); *In re Balzarini*, 21 U.S.P.Q.2d 1892 (B.P.A.I. 1991) ("While the *in vitro* testing performed on these anti-viral compounds appears to be useful as a screening tool in order to determine which of these anti-viral compounds are *candidates* for further testing to determine if they possess *in vivo* utility, the *in vitro* tests were not predictive of *in vivo* efficacy."); *cf. Novartis Consumer Health Inc. v. Johnson & Johnson – Merck Consumer Pharmaceuticals Co.*, 62 U.S.P.Q.2d 1757 (3d Cir. 2002) ("The acid neutralization capacity ('ANC') [*in vitro*] does not, however, represent an antacid's effectiveness in the human body (*i.e.*, '*in vivo*'), or its ability

to relieve the systems of acid reflux, because other factors – such as rate of gastric emptying, rate of secretion of acid, and degree of mixing between the antacid and gastric contents – all bear on the antacid's efficacy."). And Applicant notes that the citation of the plethora of additional references in support of the instant ground of rejection does nothing to increase the evidence that the skilled worker would have had such a reasonable expectation of success (*i.e.*, no evidence whatsoever).

Moreover, the Office Action provided no support, either factual or legal, for the assertion that "[o]ne skilled in the art would *always* [which appears unlikely] be motivated to extend *in vitro* methods of treating tumor cells to *in vivo* methods of treating patients with tumors . . . ." In fact, skilled artisans would not necessarily have believed that a method that had been successful in causing a chemotoxic response in tumor cells *in vitro* would be successful in treating tumor cells *in vivo*. On the contrary, there is ample evidence that the skilled worker would have come to the exact opposite conclusion, that such *in vitro* methods would *not* have been successful when applied *in vivo*. *In vitro* systems are "inadequate at addressing the issues of tumor cell heterogeneity, drug distribution, drug bioactivation, and host toxicity." *Cancer, Principles & Practice of Oncology* 304 (Vincent T. DeVita *et al.* eds., 6th ed. 2001) (attached as Appendix A). As an example that is significant for the present case, the ability to induce apoptosis had been identified as an attractive target for therapeutic intervention, but "infusion of TNF-α [to induce apoptosis] causes a lethal inflammatory response resembling septic shock, . . . and infusion of agonistic anti-Fas antibody causes lethal hepatic apoptosis." *Id.* at 118-19 (attached as Appendix B). *See also Harrison's Principles of Internal Medicine* 536 (Eugene Braunwald *et al.* eds., 15th ed. 2001) (attached as Appendix C) ("While apoptotic mechanisms are important in regulating cellular proliferation and the behavior of tumor cells *in vitro*, *in vivo* it is unclear whether all of

the actions of chemotherapeutic agents to cause cell death can be attributed to apoptotic mechanisms."). Therefore, clearly, there is more to the consideration of treating tumors *in vivo* than success against tumor cells growing *in vitro*.

Notwithstanding the art-recognized uncertainty of *in vivo* treatment of tumor cells, Applicant contends that the difference between the cited art and the claimed invention is not "one of *in vitro* versus *in vivo* exposure of tumor cells to a therapeutic agent," despite the improper framing of the issue Even if (and there is *no* evidence of record supporting this supposition) "[o]ne of skill in the art [were] always [] motivate[d] to extend *in vitro* methods of treating tumor cells to *in vivo* methods of treating patients with tumors," it is of absolutely no relevance to the question of whether the pending claims are obvious over Bacus I. The present invention is concerned with determining whether an individual *actually responded* to treatment with a chemotherapeutic or chemopreventive agent by measuring markers associated with senescence, apoptosis, or terminal differentiation. As such, treating cells in culture, *i.e.*, *in vitro*, is immaterial to an analysis of the present claims, and again underscores the Office Action's failure to consider the claimed invention as a whole.

In addition, the Office Action acknowledges that Bacus I merely teaches a method for "determining the effectiveness of a therapeutic agent in the treatment of cancer by measurement [of] the ability of the therapeutic agent to induce *terminal differentiation*," and that the method requires the measurement of "markers for *terminal differentiation*." *Office Action* at 3 (emphasis added). However, despite repeatedly reminding Applicant that the species being currently examined is apoptosis, *see, e.g., id.* at 7, the Office Action ignores the fact that Bacus I does not teach the measurement of markers associated with apoptosis. Instead, the Office Action makes the unsupported assertion that "the induction of apoptosis in breast cancer cells as a result of

chemotherapy would result in a stabilization and reduction of a cell population which would fall under the definition of 'terminal differentiation' set forth in Bacus [I]." *Id.* at 5. However, the section of Bacus I cited by the Office Action referred to measuring the cessation of cell proliferation as "yet another measure of the extent of terminal differentiation." *Bacus I*, column 11, lines 53-61. In fact, even the references cited by the Office Action recognize the distinction between apoptosis and termination differentiation. For example, Warri teaches that anticancer compounds can "induce tumor regression" that "can involve both an enhanced cell death and arrested cell proliferation." *Warri* at 1412. Warri continues to explain that cell death can be "caused either by necrosis or by an active process as a response to a specific stimulus (or lack of the stimulus) that leads to elimination of a cell population," referred to as apoptosis. *Id.* Nevertheless, because Applicant recognizes that apoptosis is merely an elected species for initial prosecution, and that because the non-elected species will be considered upon allowance of a generic claim, Applicant will continue to point out the differences between the cited art and all three identified species.

Further in support of the obviousness rejection, the Office Action cites additional references in an attempt to provide the required reasonable expectation of success for using the method of Bacus I to practice the claimed methods for determining a response to a chemotherapeutic or chemopreventive agent to an individual *in vivo*. However, none of these additional references provide the missing limitation(s) of removing a tissue or cell sample from an individual both before and after treatment (i.e., two separate samples from two different times both before and after treatment, thereby providing two qualitatively- as well as temporally-different samples) in order to determine the expression of a biological marker after exposure of

the individual to the chemotherapeutic or chemopreventive agent. None of the references provide the requisite expectation of success for modifying Bacus I.

In the context of the proper analytical framework for determining whether the claimed invention is non-obvious, none of the secondary references remedy the deficiencies of the primary Bacus I reference. Lebwohl was cited for describing that "the combined administration of Herceptin and doxorubicin result in a higher response rate and prolongs the time to disease progression when compared to chemotherapy alone" (*Office Action* at 4), and Fornier was cited for teaching "that clinical studies are underway in the treatment of breast cancer by the combined administration of Herceptin and Taxol." *Id.* The claimed invention is not directed at method of treatment claims, however, and regardless of whether Lebwohl and Fornier teach "recent clinical trails using combinations of Herceptin with Taxol and doxorubicin," as the Office Action asserts (*Id.* at 5), the particular chemotherapeutic or chemopreventive agent is not a limitation in the claimed methods. In fact, the Office Action acknowledges, at page 20, that the instant claims "do not dictate what type of therapy is to be monitored." At least for these reasons the Lebwohl and Fornier references are irrelevant to the obviousness determination of the present invention. Even if they could be taken as motivating for the skilled worker to desire to monitor the results of chemotherapeutic treatment *in vivo* (a generic desire for any potential chemotherapeutic agent neither required to evaluate the patentability of the pending claims nor supported by any specific evidence of record), the references would not motivate the skilled worker to develop the claimed assay, and thus do not support the asserted obviousness rejection.

The Office Action also cites Warri for teaching "that methods for treating breast cancer should target the induction of apoptosis to breast cancer cells" (*Id.* at 4); the Office Action's reliance on this reference is understood as indicating that the skilled worker would be motivated

to assay for apoptosis to determine whether the treatment was inducing apoptosis. Wu is cited for teaching "that apoptosis is a valuable marker for response in patients having primary or adjuvant chemotherapy for breast cancer." *Id.* Finally, Bacus II is cited as teaching "that Taxol and doxorubicin affect apoptotic signaling in breast cancer cells by different mechanisms," that "inhibition of PI-3 resulted in the inhibition of doxorubicin induced cell cycle arrest," and that "Herceptin inhibits PI-3 kinase." While perhaps scientifically interesting results, the Office Action fails to explain how a determination of the molecular consequences of anticancer treatment is relevant to the instantly-claimed invention. The Office Action concludes that one skilled in the art would have been motivated with a reasonable expectation of success to modify the teachings of Bacus I to practice the claimed invention because Bacus II calls "into question the interaction with Herceptin on the apoptotic pathways utilized by doxorubicin and Taxol," Warri discloses "the correlation between the induction of apoptosis and response to chemotherapy of breast cancer," and Wu discloses "the correlation between the induction of apoptosis and response to chemotherapy of breast cancer." While true that all of these references are directed towards the biochemical bases for the mode of action of drugs such as doxorubicin, Taxol and Herceptin used in treating breast cancer, there is no teaching or suggestion in any of these references that tumor tissue could or should be assayed before and after treatment with any or all of these drugs, or that such assays could meaningfully assess whether the drugs have been effective by assaying expression of apoptosis-, senescence- or terminal differentiation-related markers in such tumor tissue. There is also no teaching or suggestion that such an assay would be useful for monitoring the effectiveness of these (or any other) anticancer drugs, nor is there any disclosure in these references that would motivate the skilled worker to assay these markers to assess the effectiveness of any chemotherapeutic treatment.

Applicants further contend that not only is their invention non-obvious by statute, it was not "obvious to try" the claimed approach in view of the cited art. The Federal Circuit has identified two kinds of error that fall within the category of "obvious to try." One of these errors, and the one that is germane to the present case, is when "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). This situation "exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *In re Eli Lilly*, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990).

The Board has applied this obvious-to-try standard in overturning improper obviousness rejections. For example, in *In re Obukowicz*, 27 U.S.P.Q.2d 1063 (B.P.A.I. 1992), the Board found that a reference regarding combating mosquitoes using genetically engineered "natural pond microflora," when combined with advice regarding incorporation of a mosquito toxin gene into plasmids of various bacteria did not render obvious a method of combating mosquitoes by using plant-colonizing bacteria with that particular gene incorporated into its chromosome. The Board concluded that there was no "suggestion to insert the gene into the *chromosome* of bacteria *and* apply that bacteria to the plant environment in order to protect the plant." *Id.* at 1065. "At best, the [suggestion] is but an invitation to scientists to explore a new technology that seems a promising field of experimentation" *Id.* ("We recognize that given the teachings in appellants' specification regarding incorporation of the gene into the chromosome and utilizing the bacteria

in the plant environment, one can theoretically explain the technological rationale for the claimed invention using selected teachings from the references. This approach, however, has been criticized by our reviewing court as hindsight reconstruction."). As a further example, in *In re Primakoff*, 64 U.S.P.Q.2d 1848 (B.P.A.I. 2001) (unpublished), the Board reversed an examiner's obviousness rejection of claims drawn to vaccines comprising sperm surface protein purified from a mammal other than guinea pig. The examiner had identified a reference to vaccines with the guinea pig sperm surface protein *and* a suggestion that the human functional analogue of the protein would be a candidate for an effective contraceptive immunogen. However, the Board found that because the reference did not disclose whether a human functional analogue existed, whether it would be structurally similar to the guinea pig protein, or how to purify the protein, it merely provided "'a general disclosure [which] may pique the scientist's curiosity, . . . [but without] a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued," the claimed invention was merely "'obvious to try.'" *Id.* at 1850-51. Here, the Office Action does not even assert that there was a suggestion to achieve the claimed invention, but merely a general and generic (and both unsupported and unspecified) "motivation" provided by the cited prior art. As is (at best) the case here, whether it might have been "obvious to try" the approach taken by the inventor in this application is insufficient to support the asserted obviousness rejection.

Assuming (without conceding the point) that the teachings of the Warri, Wu, and Bacus II references were directed towards targeting apoptosis in the treatment of breast cancer or determining the correlation (if any) between inducing apoptosis and response to breast cancer chemotherapy, it may in fact have been obvious to try monitoring the increase in markers of apoptosis in an individual receiving such chemotherapy for breast cancer. However, there is no

cited prior art that provided *specific* guidance for the *particular* form of the invention, or how to achieve it, prior to Applicant's disclosure. Specifically, the cited art contains no teachings, much less suggestion that a response to administration of a chemotherapeutic or chemopreventive agent could be detected or monitored by collecting tissue of cell samples before and after exposing the individual to the agent, and using immunohistochemistry to determine whether expression of biological markers associated with senescence, apoptosis, or terminal differentiation were increased after exposure. In fact, it was Applicant's disclosure that first demonstrated markers to senescence, apoptosis, or terminal differentiation *could be* observed after an individual is treated with a chemotherapeutic or chemopreventive agent by comparing samples removed from the individual both before and after the individual is exposed to the compound. *See, e.g., '119 application, examples 4 and 6.* In the absence of such teaching in the cited art, the skilled artisan could have had no reasonable expectation of success for achieving the claimed invention by combining the cited references, absent Applicant's disclosure. Therefore, the citation of Bacus I, in view of Warri, Wu, and Bacus II, and even in view of Fornier and Lebwohl, failed to render the present invention obvious, as required by 35 U.S.C. § 103(a).

For the reasons set forth above, none of the references cited in support of this ground of rejection, Bacus I, Warri, Wu, Fornier, Lebwohl, and Bacus II, taken either alone or in any combination, disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemoprevention agent to an individual. Accordingly, Applicant respectfully requests that the Examiner withdraw this ground of rejection and pass these claims to issue.

Claims 1-3 , 5, and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Bacus I in view of Bacus II, Warri, Wu, Fornier, and Lebwohl (all cited above) and further in view of Caffo *et al.* (Clinical Cancer Res., 1996, vol. 2, pp. 1591-1599) ("Caffo"), the abstract of el-Deiry *et al.* (Cancer Res. 1995, Vol. 55, pp. 2910-2919) ("el-Deiry"), the abstract of Thor *et al.* (J. Nat'l Can. Inst., 1992, Vol. 84, pp. 845-855) ("Thor"), and the abstract of Shetty *et al.* (Leukemia Res., 1996, vol. 20, pp. 11-12) ("Shetty"). Applicants respectfully traverse this rejection.

Applicant provided an analysis of the scope and content of the prior art cited by the Office Action in the Response to Office Action Mailed June 4, 2004, filed December 4, 2004. Applicant reiterates that none of the references cited in support of this ground of rejection, Bacus I, Bacus II, Warri, Wu, Fornier, Lebwohl, Caffo, el-Deiry, Thor, and Shetty, taken either alone or in any combination, disclose, either individually or in combination, the instantly claimed method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Once again, Applicant asserts, at the least, that the Office Action has impermissibly failed to consider the claimed invention as a whole, and has failed to establish that even if the references could have been combined there would have been no reasonable expectation of success of arriving at the claimed invention before the Applicant's disclosure. At best, the Office Action has established that the claimed invention was obvious to try, which has been expressly rejected as the standard under 35 U.S.C. § 103. M.P.E.P. § 2145(X)(B).

The deficiencies of several of these references (Bacus I, Bacus II, Warri, Wu, Fornier, and Lebwohl) in supporting an obviousness rejection of these claims has been set forth above, and applies with equal force with regard to this separately-enunciated ground of rejection and will not be repeated here except by reference. None of the additionally-cited references, taken alone or in

any combination with the earlier-discussed references, teach or suggest the instantly claimed method. The deficiencies of Bacus I, Bacus II, Warri, Wu, Fornier, and Lobwohl are not overcome by the combination with the other cited art.

All of the additional references cited in support of this separate ground of rejection teach antibodies for detecting molecular species expressed in certain cells. el-Deiry is cited for teaching "that antibodies to human p21 can be used in immunohistochemical analysis to monitor the effects of radiation induced damage." Thor is cited for teaching "that antibodies to human p53 can be used in immunohistochemical analysis to detect p53 in archival samples of breast carcinomas." Shetty is cited for teaching "that antibodies to human TGF-beta can be used in immunohistochemical analysis to monitor the expression of TGF-beta in cells of myelodysplastic syndromes." The list of what these additional references do not provide is considerably longer than the list of what they do provide. The availability of certain tools for detecting expression of certain gene products does not provide any teachings of what *should be* assayed, or when or after what treatment or whether the assayed sample should be an *in vivo* or *in vitro* sample. Even the Office Action is compelled to concede that el-Deiry, Thor, and Shetty are relied upon merely to demonstrate that antibodies directed to p21 and p53 can bind to p21 and p53 in tissue samples. However, Applicant has not claimed such antibodies, or argued that antibodies to p21 and p53 did not exist prior to the present invention, or that such antibodies would not be expected to bind their epitopes in tissue samples. Indeed, the invention is not drawn to any specific antibodies that can be used in immunohistochemical staining, but rather to the use of such antibodies in methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. As such, these three references are irrelevant to the obviousness determination of the present invention.

Further, Warri is additionally cited in this rejection (in addition to the teachings cited in the obviousness rejection addressed above) for teaching "that mRNA for TGF-beta is a biological marker for apoptosis." Initially, there is no basis for assuming that "[i]t is reasonable to conclude that TGF-beta protein was elevated as a result of the elevation of TGF-beta mRNA," as the Office Action asserts. The art recognizes that, particularly in eukaryotic cells there is not a direct correlation between transcription (RNA production) and translation (protein production), since the two (unlike in bacteria), are uncoupled inside the cell. Further, although it is true that antibodies directed to TGF-beta existed in the art before the priority date, nowhere has Applicant argued that TGF-beta is not a biological marker for apoptosis, nor claimed any such antibodies *per se*. Indeed, the invention is not drawn to any specific antibodies that can be used in immunohistochemical staining, but rather to the use of such antibodies (whether or not they are in the prior art) in methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Applicant respectfully submits that the Warri teaching that mRNA for TGF-beta is a biological marker for apoptosis is irrelevant to the obviousness determination of the present invention.

The Caffo reference was cited for teaching "that the p21/p53 phenotype may be of clinical relevance concerning the response to chemotherapy/hormone therapy and that the p21 negative/p53 positive phenotype could correspond to a situation where p53 is expressed but lacks transcriptional activity because of mutational or functional inactivation and that this phenotype reflexes the complete abrogation of p53 function." *Office Action* at p. 12. Further, Caffo is cited as teaching "that in p21 negative/p53 positive cases the tumor cells have an impaired G1 checkpoint and may not be able to activate the apoptotic cascade in response to DNA damaging chemotherapy and thus can be more prone to treatment failure by conventional therapy." *Id.* The

Office Action concludes that one skilled in the art would have been motivated with a reasonable expectation of success to modify the teachings of Bacus I to practice the claimed invention because Caffo teaches "the importance of the p21 and p53 phenotypes of breast tumors in the response to chemotherapy," and the unsupported assertion that "one skilled in the art would conclude that if the remaining tumor cells were p21 negative/p53 positive, chemotherapy should be stopped." *Id.* at 12-13. Applicant respectfully contends that the Caffo reference, while disclosing important aspects of p21 and p53 expression in tumor cells, is not relevant to the claimed invention since there is no teaching that the observed biochemical properties of p21 and p53 in Caffo have been validated as determinative markers for chemotherapeutic treatment, or that those having skill in the art would accept Caffo's speculations as being sufficient to make therapeutic choices based upon them. Nor are the claimed methods dependent on Office Action's unsupported assertions.

A combination of the teachings of Bacus I and Caffo could do no more than make it obvious to try assaying "for both p21 and p53 in patients undergoing treatment with [an] anti-tumor therapeutic agent targeted to induce apoptosis in order to determine if in fact said patients ha[ve] tumor cells which were resistant to the treatment." *Id.* at 13. However, there is no cited art that provides specific guidance for the particular form of the invention, or how to achieve it. Specifically, there was no teaching or suggestion in the cited art that a response to administration of a chemotherapeutic or chemopreventive agent could be determined by collecting tissue or cell samples before and after exposing the individual to the agent, and using immunohistochemistry to determine whether expression of the biological markers associated with senescence, apoptosis, or terminal differentiation (including p21 and p53) were increased after exposure. In fact, it was Applicant's disclosure that first demonstrated that an increase in markers to senescence,

apoptosis, or terminal differentiation could be observed after an individual is treated with a chemotherapeutic or chemopreventive agent by comparing samples removed from the individual both before and after the individual is exposed to the compound. *See, e.g., '119 application, examples 4 and 6.* Without Applicant's disclosure, a skilled artisan would have had no reasonable expectation of success for combining the cited references, even if there was sufficient motivation to do so. Therefore, the citation of Bacus I, in view of Warri, Wu, and Bacus II, further in view of Caffo, and even in view of Fornier, Lebwohl, el-Deiry, Thor, and Shetty, at best made the claimed invention obvious to try, but failed to render the present invention obvious, as required by 35 U.S.C. § 103(a).

For the reasons set forth above, Bacus I, Bacus II, Warri, Wu, Fornier, Lebwohl, Caffo, el-Deiry, Thor, and Shetty do not disclose, either individually or in combination, nor render obvious a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests that the Examiner withdraw this ground of rejection and pass these claims to issue.

Claims 1-3 , 5, and 6 are yet again rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Bacus I in view of Bacus II, Warri, Wu, Fornier, and Lebwohl (all cited above), and further in view of Hochhauser (Anti-Cancer Drugs, 1997, Vol. 8., pp. 903-910) ("Hochhauser"), the abstract of Ohtani *et al.* (Cancer, 1999, vol. 85, pp. 1711-1718) ("Ohtani"), and the abstract of Emig *et al.* (British J. of Cancer, 1998, Vol. 78, pp. 1661-1668) ("Emig"). Applicants respectfully traverse this rejection.

Applicant provided an analysis of the scope and content of the prior art cited by the Office Action in the Response to Office Action Mailed June 4, 2004, filed December 4, 2004.

Applicant reiterates that none of the references cited in support of this ground of rejection, Bacus I, Bacus II, Warri, Wu, Fornier, Lebwohl, Hochhauser, Ohtani, and Emig, taken either alone or in any combination, disclose, either individually or in combination, the instantly claimed method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. As with above, Applicant asserts, at the least, that the Office Action has impermissibly failed to consider the claimed invention as a whole, and has failed to establish that even if the references could have been combined there would have been no reasonable expectation of success of arriving at the claimed invention before the Applicant's disclosure. At best, the Office Action has established that the claimed invention was obvious to try, which has been expressly rejected as the standard under 35 U.S.C. § 103. M.P.E.P. § 2145(X)(B).

The deficiencies of several of these references (Bacus I, Bacus II, Warri, Wu, Fornier, and Lebwohl) in supporting an obviousness rejection of these claims has been set forth above, applies with equal force with regard to this separately-enunciated ground of rejection and will not be repeated here except by reference. None of the additionally cited references, taken alone or in any combination with the earlier-discussed references, teach or suggest the instantly claimed method. The teachings and deficiencies, as related to the present invention, of Bacus I, Bacus II, Warri, Wu, Fornier, Lebwohl are discussed in detail above. The deficiencies of Bacus I, Bacus II, Warri, Wu, Fornier, Lebwohl are not overcome by the combination with the other cited art.

Now once again the Office Action cites a number of references that disclose the use of reagents, specifically antibodies, for the detection of expression of markers for apoptosis, senescence or terminal differentiation. Ohtani is cited for teaching "that antibodies to human p27 can be used in immunohistochemical analysis to monitor the expression of p27 in gastric cancer cells and that decreased levels of p27 are indicative of decreased rates of apoptosis in said cells."

Emig is cited for teaching "antibodies to human p16 can be used in immunohistochemical analysis to monitor the expression of p16 in breast cancer." The availability of certain tools for detecting expression of certain gene products does not provide any teachings of what *should be* assayed, or when or after what treatment or whether the assayed sample should be an *in vivo* or *in vitro* sample. Even the Office Action is forced to concede that Ohtani and Emig are relied upon merely to demonstrate the availability of "antibodies to human p16 and p27 and [the] usefulness of said antibodies for immunohistochemistry." However, Applicant has not argued that antibodies to p16 and p27 did not exist prior to the present invention. Indeed, the invention is not drawn to specific antibodies that can be used in immunohistochemical staining, but rather to the use of such antibodies in methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. As such, these two references are irrelevant to the obviousness determination of the present invention.

Additionally, the Office Action further cites Hochhauser as teaching "that alterations in cell cycle genes can sensitize cells to apoptosis following treatment with chemotherapeutic agents," that "induction of p16 expression results in reversible cell cycle arrest which renders cells resistant to a variety of chemotherapeutic agents including methotrexate, cisplatin, and vincristine," and that "expression of p27 in tumors is related to acquired drug resistance to chemotherapeutic agents." *Office Action* at 16. The Office Action uses this disclosure, that relates merely to the biochemical properties of certain gene products known to be associated with apoptosis, to conclude without other support that one skilled in the art would have been motivated with a reasonable expectation of success to modify the teachings of Bacus I to practice the claimed invention, because Hochhauser teaches "the inverse relationship between expression of p27 and p16 and the induction of apoptosis by chemotherapeutic agents . . . ." *Id.* The Action

fails to establish that knowledge concerning the biochemical activity of molecules (p16 and p27) known to be associated with apoptosis and senescence would teach, suggest, or motivate the skilled worker to attempt to detect or monitor the effectiveness of chemotherapeutic treatment using the claimed method, and thus the addition of these references to the plurality of references arrayed against the exact same claims in the several other grounds of rejection based on 35 U.S.C. § 103 does nothing to further support the asserted obviousness rejection. The citation of Bacus I, in view of Warri, Wu, and Bacus II, further in view of Hochhauser, and even in view of Fornier, Lebwohl, Ohtani, and Emig thus fails to render the present invention obvious, as required by 35 U.S.C. § 103(a).

For the reasons set forth above, Bacus I, Bacus II, Warri, Wu, Fornier, Lebwohl, Hochhauser, Ohtani, and Emig do not disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests that the Examiner withdraw this ground of rejection and pass these claims to issue.

Claims 1, 2, 4, and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Meyn *et al.* (*AntiCancer Drugs*, 1995, vol. 6, pp. 443-450) ("Meyn") in view of Riss (U.S. 6,350,452) ("Riss") and Bjorklund *et al.* (WO 99/16789) ("Bjorklund") and Schlossman *et al.* (U.S. 5,935,801) ("Schlossman") and Desjardins (U.S. 5,972,622) ("Desjardins"). Applicants respectfully traverse this rejection.

Applicant provided an analysis of the scope and content of the prior art cited by the Office Action in the Response to Office Action Mailed June 4, 2004, filed December 4, 2004. Applicant reiterates that none of the references cited in support of this ground of rejection, Meyn,

Riss, Björklund, Schlossman, and Desjardins, taken either alone or in any combination, disclose, either individually or in combination, the instantly claimed method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual.

These references, providing yet another ground of obviousness rejection using different prior art than the previously-asserted three obviousness rejections, are not discussed in the Office Action with regard to the teachings of the cited references in the previous rejections. The Office Action did not combine these references with the teachings of the aforesaid plurality of references. Therefore, Applicant understands that the Office Action is hereby asserting a separate and independent ground of rejecting the pending claims for obviousness based on these references, and that the newly-cited references are not being combined with the other cited references discussed above. As before, Applicant asserts, at the least, that the Office Action has impermissibly failed to consider the claimed invention as a whole, and has failed to establish that even if the references could have been combined there would have been no reasonable expectation of success or arriving at the claimed invention before the Applicant's disclosure. At best, the Office Action has established that the claimed invention was obvious to try, which has been expressly rejected as the standard under 35 U.S.C. § 103. M.P.E.P. § 2145(X)(B).

Specifically, in this ground of rejection the Office Action cites Riss as teaching "antibodies that recognize an epitope of the PARP protein formed by cleavage of said protein by caspases." Bjorklund is cited for teaching "a method for detecting early apoptotic changes in epithelial cells comprising contacting said cells with the M30 antibody which binds to an epitope of keratin 18 that is exposed after cleavage by caspases." Schlossman is cited for teaching "an antibody which binds to an epitope localized on the membrane of mitochondria, 7A6, wherein said epitope is present only in cells undergoing apoptosis." Desjardins is cited for teaching "anti-

GP46 antibodies, which specifically target apoptotic cells." With regard to these references, the Office Action reiterates its assertion that one of ordinary skill in the art at the time the invention was made would have been motivated to "use any of the antibodies taught by Riss, Bjorklund, Schlossman, or Desjardins in a method of monitoring the efficacy of chemotherapy in an individual, wherein a sample of cells or tumor tissue was taken from said individual before and after the administration of a chemotherapeutic drug, and wherein the analysis was done by means of ELISA or image analysis." *Office Action* at 19. In addition, the Office Action asserts that "[o]ne of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teaching of Meyn on apoptosis as a feature of tumor response to chemotherapy *in vivo*, and the heterogeneity of apoptotic response between different tumor types and to different cytotoxic agents." *Id.* (Applicant notes that the Meyn reference itself teaches that apoptotic response is heterogeneous, which would have taught away from, and eliminated the skilled worker's reasonable expectation of success regarding using apoptosis detection as a reliable parameter for assessing the success or failure of *in vivo* chemotherapy.) Further, the Office Action makes the unsupported assertion that "[o]ne of skill in the art would be motivated to substitute the assay based on antibody binding for the conventional assays of tumor size measurement because Desjardins teaches that said conventional assays require at least a month of treatment before a detectable difference would be measured." *Id.* at 19-20. Of course, what the Office Action does not support is the implied direct correlation between tumor size (which is certainly a reliable indicator of a drug eliciting a successful anticancer effect) and an increase or decrease in a marker detected by an antibody.

The question once again is whether the cited references teach, suggest, or motivate one of ordinary skill to accomplish the claimed invention, when that invention is considered as a whole

and not as a combination of individual features, limitations, or components. In this case, that question is not whether the differences themselves would have been obvious, *i.e.*, whether it would have been obvious to substitute the assay based on antibody binding for the conventional assay of tumor size measurement, but rather whether the claimed invention as a whole would have been obvious in view of the cited art. In this rejection, the Office Action reduces the question, improperly, to whether it would be obvious to use immunohistochemical methods to monitor cellular markers, or even markers of apoptosis, in replacement for physical observation of tumor size. This is not the invention, however; the invention rather is an assessment of the response of an individual to treatment with a chemotherapeutic or chemopreventive agent using immunohistochemical techniques and methods taught and claimed by Applicant. By improperly focusing on the obviousness of the *differences* between the cited art and the claimed invention (regarding measuring apoptosis), the Office Action has failed to consider the invention as a whole, and thus has failed to establish a *prima facie* case of obviousness.

The Office Action concedes that Riss, Bjorklund, Schlossman, and Desjardins are relied upon to demonstrate antibodies that *could be* used (without citing support for the proposition) in determining whether apoptosis has been induced in tumor cells, and thus which *could be* used in the claimed invention. However, Applicant has not claimed such antibodies, or argued that antibodies directed to markers of apoptosis did not exist prior to the present invention, or that such antibodies would not be expected to bind their epitopes in tissue samples. Indeed, the invention is not drawn to specific antibodies that can be used in immunohistochemical staining, but rather to the use of such antibodies in methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. As such, these four references are irrelevant to the obviousness determination of the present invention. Although a method

claim may require underlying tools to be operative, the mere existence of the tools themselves does not render such methods claims obvious absent affirmative teaching, suggestion or motivation, coupled with a reasonable expectation of success, of the claimed method. This is precisely the case here.

Even if the assertions in the Office Action that one of ordinary skill in the art would have been motivated "to use any of the antibodies taught by Riss, Björklund, Schlossman, and Desjardins in a method of monitoring the efficacy of chemotherapy in an individual," based on "the teaching of Meyn on apoptosis as a feature of tumor response to chemotherapy *in vivo*, and the heterogeneity of apoptotic response between different tumor types and to different cytotoxic agents," there was no teaching, suggestion, or motivation coupled with a reasonable expectation for success in making the claimed invention. There was no teaching in the cited art that provided any guidance for the claimed method, or any way to achieve it. Specifically, no one had taught, much less suggested, that an apoptotic response to administration of a chemotherapeutic or chemopreventive agent could be assayed by collecting tissue or cell samples before and after exposing the individual to the agent, and using immunohistochemistry to determine whether expression of the biological markers associated with senescence, apoptosis, or terminal differentiation were increased after exposure. In fact, it was Applicant's disclosure that first demonstrated that an increase in markers to senescence, apoptosis, or terminal differentiation *could be* observed after an individual is treated with a chemotherapeutic or chemopreventive agent by comparing samples removed from the individual both before and after the individual is exposed to the compound. *See, e.g., '119 application, examples 4 and 6.* Without Applicant's disclosure, a skilled artisan would have no reasonable expectation of success for combining the cited references, and even if they were combined these references do not support an obviousness

determination of the claimed invention. Therefore, the citation of Meyn, in view of Riss, Björklund, Schlossman, and Desjardins fail to render the present invention obvious, as required by 35 U.S.C. § 103(a).

For the reasons set forth above, Meyn, Riss, Björklund, Schlossman, and Desjardins do not disclose, either individually or in combination, nor render obvious a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests that the Examiner withdraw this ground of rejection and pass these claims to issue.

Claims 1, 2, and 4-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Meyn in view of Riss, Bjorklund, Schlossman, and Desjardins (all cited above), and further in view of Bacus I (also cited above). Applicant respectfully traverses this rejection.

Applicant provided an analysis of the scope and content of the prior art cited by the Office Action in the Response to Office Action Mailed June 4, 2004, filed December 4, 2004. Applicant reiterates that none of the references cited in support of this ground of rejection, Meyn, Riss, Björklund, Schlossman, Desjardins, and Bacus I, taken either alone or in any combination, disclose, either individually or in combination, the instantly claimed method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual.

Once again, the Action asserts an obviousness rejection based on yet another combination of the cited art. The deficiencies of several of these references (Meyn, Riss, Björklund, Schlossman, and Desjardins) in supporting an obviousness rejection of these claims has been set forth above, and applies with equal force with regard to this separately-enunciated ground of

rejection and will not be repeated here except by reference. Further, Bacus I, taken alone or in any combination with the earlier-discussed references, does not teach or suggest the instantly claimed method. The deficiencies of Meyn, Riss, Björklund, Schlossman, and Desjardins are not overcome by the combination with Bacus I. In fact, the Office Action apparently is only citing Bacus I in the present rejection as teaching the embodiments recited in claim 6, as well as the reasonable expectation of success for claim 6. Bacus I is cited as teaching "that cell sample[s] can be stained with an antibody and an additional DNA stain, and the digitization of two filtered images of the single sample, one for each specific stain, allows for the summation of the optical density value for the DNA satin and the optical density value for the antibody stain." *Office Action* at 21. The Office Action therefore concludes that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to include a DNA stain with the detectably labeled antibody and perform image analysis," and that they would have "a reasonable expectation of success by the teaching of Bacus on the inclusion of a DNA stain to determine the total number of cells in the sample." *Id.*

However, the addition of Bacus I, in combination with the other references could do no more than make it obvious to try the inclusion of a DNA stain with the detectably labeled antibody and perform image analysis. There is no cited art newly provided in support of this ground of rejection that provides specific guidance for the particular form of the present invention, or how to achieve it. Specifically, the cited art contains no teaching, much less suggestion, that a response to administration of a chemotherapeutic or chemopreventive agent could be detected or monitored by collecting tissue of cell samples before and after exposing the individual to the agent, and using immunohistochemistry to determine whether expression of biological markers associated with senescence, apoptosis, or terminal differentiation were

increased after exposure, much less the further limitations of claim 6. In fact, it was Applicant's disclosure that first demonstrated markers to senescence, apoptosis, or terminal differentiation could be observed after an individual is treated with a chemotherapeutic or chemopreventive agent by comparing samples removed from the individual both before and after the individual is exposed to the compound. *See, e.g., '119 application, examples 4 and 6.* In the absence of such teaching in the cited art, the skilled artisan could have had no reasonable expectation of success for achieving the claimed invention by combining the cited references, absent Applicant's disclosure, even if there was motivation to do so. Therefore, the citation of Meyn, in view of Riss, Björklund, Schlossman, and Desjardins, and further in view of Bacus I failed to render the present invention obvious, as required by 35 U.S.C. § 103(a).

Further, the Office Action asserts that Meyn teaches the "heterogeneity of apoptotic response between different tumor types and to different cytotoxic agents," and that this is "ample motivation to monitor the degree of apoptosis in response to every individual patient being administered cytotoxic agents." *Office Action* at 24. Therefore, the Office Action concludes, "there is a strong motivation to monitor the individual response after a treatment," because a skilled artisan "would want to be assured that an efficacious response were being attained by said *in vivo* treatment." *Id.* Contrary to the Office Action's assertion, however, the teaching that the apoptotic response is heterogeneous would not provide the requisite motivation, but rather would have taught away from the claimed invention, because a skilled artisan would not have had a reasonable expectation of success for using apoptosis detection as a reliable parameter for assessing the success or failure of *in vivo* chemotherapy.

For the reasons set forth above, Meyn, Riss, Björklund, Schlossman, Desjardins, and Bacus I do not disclose, either individually or in combination, nor render obvious, a method for

determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests that the Examiner withdraw this ground of rejection and pass these claims to issue.

Claims 1, 2, 4 and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Meyn in view of Riss, Björklund, Schlossman, and Desjardins (all cited above), and further in view of Booth et al. (Apoptosis, 1996, vol. 1, pp. 191-200) ("Booth"), the abstract of Shen *et al.* (Cancer, 1998, vol. 82, pp. 2373-2381) ("Shen"), the abstract of Hiraishi *et al.* (Glycobiology, 1993, vol. 3, pp. 381-390) ("Hiraishi"), the abstract of Cutrona *et al.* (J. Experimental Medicine, 1995, vol. 181, pp. 699-711) ("Cutrona"), and the abstract of Frankfurt *et al.* (Anti-Cancer Res., 1996, vol. 16, pp. 1979-1988) ("Frankfurt"). Applicants respectfully traverse this rejection.

Applicant provided an analysis of the scope and content of the prior art cited by the Office Action in the Response to Office Action Mailed June 4, 2004, filed December 4, 2004. Applicant reiterates that none of the references cited in support of this ground of rejection, Meyn, Riss, Björklund, Schlossman, Desjardins, Booth, Shen, Hiraishi, Cutrona, and Frankfurt, taken either alone or in any combination, disclose, either individually or in combination, the instantly claimed method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual.

The deficiencies of several of these references (Meyn, Riss, Björklund, Schlossman, and Desjardins) in supporting an obviousness rejection of these claims has been set forth above, and applies with equal force with regard to this separately-enunciated ground of rejection and will not be repeated here except by reference. None of the additionally-cited references, taken alone or in

any combination with the earlier-discussed references, teach or suggest the instantly claimed method. The deficiencies of Meyn, Riss, Björklund, Schlossman, and Desjardins are not overcome by the combination with Booth, Shen, Hiraishi, Cutrona, and Frankfurt.

All of the additional references cited in support of this separate ground of rejection teach antibodies for detecting markers of apoptosis. Booth is cited for teaching "that antibodies raised to the peptide DVVDADEYLIPQ [] are a useful marker of apoptotic cell in the intestinal epithelium." Shen is cited for teaching "that the Ki-67 antibody is indicative of apoptosis." Hiraishi is cited for teaching "that antibodies which bind to Ley are indicative of apoptosis." Cutrona is cited for teaching "that expression of CD10 and CD38 on the surface of lymphoma cells was indicative of said cells undergoing apoptosis." Frankfurt is cited for teaching "that monoclonal antibodies which bind to single stranded DNA are indicative of apoptosis." The availability of certain tools for detecting markers of apoptosis does not provide any teachings of what *should be* assayed, or when or after what treatment or whether the assayed sample should be an *in vivo* or *in vitro* sample.

Even the Office Action is compelled to concede that Booth, Shen, Hiraishi, Cutrona, and Frankfurt are relied upon merely to demonstrate that "alternative antibodies which specifically bind to apoptotic markers" can be used in the method of detecting apoptosis. However, Applicant has not claimed such antibodies, or argued that there were no antibodies that bind markers of apoptosis prior to the present invention, or that the antibodies disclosed in the specification were the only antibodies known at the time. Indeed, the invention is not drawn to any specific antibodies that can be used in immunohistochemical staining, but rather to use of such antibodies in methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. In fact, the instant claimed method was made

possible because of all the various antibodies that specifically bind to apoptotic markers. As such, these five references newly cited reference are irrelevant to the obviousness determination of the present invention. The citation of Meyn, in view of Riss, Björklund, Schlossman, and Desjardins, in combination with Booth, Shen, Hiraishi, Cutrona, and Frankfurt thus fails to render the present invention obvious, as required by 35 U.S.C. § 103(a).

For the reasons set forth above, Meyn, Riss, Björklund, Schlossman, Desjardins, Booth, Shen, Hiraishi, Cutrona, and Frankfurt do not disclose, either individually or in combination, nor render obvious a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests that the Examiner withdraw this ground of rejection and pass these claims to issue.

Claims 1, 2, 4 and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Meyn in view of Riss, Björklund, Schlossman, and Desjardins, and Bacus I (all cited above), and further in view of Pamukcu *et al.* (U.S. 5,852,035) ("Pamukcu"), Smith-McCune *et al.* (WO 99/24620) ("Smith-McCune"), and the abstract of Attallah *et al.* (Hepato-Gastroenterology, 1996, Vol. 43, pp. 1305-1312) ("Attallah"). Applicants respectfully traverse this rejection.

Applicant provided an analysis of the scope and content of the prior art cited by the Office Action in the Response to Office Action Mailed June 4, 2004, filed December 4, 2004. Applicant reiterates that none of the references cited in support of this ground of rejection, Meyn, Riss, Björklund, Schlossman, Desjardins, Bacus I, Pamukcu, Smith-McCune, and Attallah, taken either alone or in any combination, disclose, either individually or in combination, the instantly

claimed method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual.

The deficiencies of several references (Meyn, Riss, Björklund, Schlossman, Desjardins, and Bacus I) in supporting an obviousness rejection of these claims has been set forth above, and applies with equal force with regard to this separately-enunciated ground of rejection and will not be repeated here except by reference. None of the additionally-cited references, taken alone or in any combination with the earlier-discussed references, teach or suggest the instantly claimed method. The deficiencies of Meyn, Riss, Björklund, Schlossman, Desjardins, and Bacus I are not overcome by the combination with Pamukcu, Smith-McCune, and Attallah.

All of the additional references cited in support of this separate ground of rejection teach methods for inducing apoptosis, or measuring apoptotic cells. Pamukcu is cited for teaching "a method for treating *pre-malignant* lesions including colonic polyps and cervical dysplasia by administering compounds which induce apoptosis in said neoplastic tissues." *Office Action* at 24. Even if Pamukcu teaches the use of compounds with "individuals having pre-malignant lesions or dysplasia," as the Office Action asserts, *id.* at 25, the particular chemotherapeutic or chemopreventive agent is not a limitation in the claimed methods. Even the Office Action is compelled to concede, at page 20, that the instant claims "do not dictate what type of therapy is to be monitored." As such, Pamukcu is irrelevant to the obviousness determination of the present invention.

Further, the Office Action cites Attallah for teaching "that antibodies which bind to CK1 can be used to quantify apoptotic epithelial cells in premalignant lesions of the gastric mucosa." Again, the Office Action is compelled to concede that Attallah is relied upon to demonstrate that use of antibodies to quantify apoptosis in premalignant lesions. However, Applicant has not

claimed such antibodies, or argued that antibodies directed to markers of apoptosis did not exist prior to the present invention. Indeed, the invention is not drawn to any specific antibodies that can be used in immunohistochemical staining, but rather to the use of such antibodies in methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. As such, these Atallah is irrelevant to the obviousness determination of the present invention.

Additionally, the Office Action cites Smith-McCune for teaching "a method[] of screening for cervical dysplasia and cervical cancer comprising the measurement of apoptotic cells in cervical samples." *Office Action* at 24. Further, Smith-McCune is cited for teaching "that the apoptotic rate is unregulated in dysplastic tissue." *Id.* The Office Action concludes that one skilled in the art would have been motivated with a reasonable expectation of success to modify the teachings of Meyn, Riss, Björklund, Schlossman, and Desjardins by, among other things, "the teaching of Smith-McCune on the correlation between apoptotic rate and dysplasia."

The teaching of Smith-McCune, with or without the teaching of Pamuku and Attallah could do no more than make it obvious to try to substitute the chemopreventive agent or chemotherapeutic agents in the combination of Meyn, Riss, Björklund, Schlossman, Desjardins, and Bacus I. However, there is no cited art that provides specific guidance for the particular form of the invention, or how to achieve it. Specifically, there was no teaching or suggestion in the cited art that a response to administration of a chemotherapeutic or chemopreventive agent could be determined by collecting tissue of cell samples before and after exposing the individual to the agent, and using immunohistochemistry to determine whether expression of the biological markers associated with senescence, apoptosis, or terminal differentiation were increased after exposure. In fact, it was Applicant's disclosure that first demonstrated that an increase in

markers to senescence, apoptosis, or terminal differentiation could be observed after an individual is treated with a chemotherapeutic or chemopreventive agent by comparing samples removed from the individual both before and after the individual is exposed to the compound. *See, e.g., '119 application, examples 4 and 6.* Without Applicant's disclosure, a skilled artisan would have no reasonable expectation of success for combining the cited references, even if there was sufficient motivation to do so. Therefore, the citation of Meyn, in view of Riss, Björklund, Schlossman, Desjardins, and Bacus I, and further in view of Smith-McCune, and even in view of Pamuku and Attallah, at best made the claimed invention obvious to try, but failed to render the present invention obvious, as required by 35 U.S.C. § 103(a).

For the reasons set forth above, Meyn, Riss, Björklund, Schlossman, Desjardins, Bacus I, Pamukeu, Smith-McCune, and Attallah do not disclose, either individually or in combination, nor render obvious a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests that the Examiner withdraw this ground of rejection and pass these claims to issue.

Conclusion

In view of the above amendments and remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully Submitted,

Date: August 26, 2004

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